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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,825	05/23/2001	Robert E. Krall	PROV1110-3	9432
28213	7590	07/27/2004	EXAMINER	
GRAY CARY WARE & FREIDENRICH LLP 4365 EXECUTIVE DRIVE SUITE 1100 SAN DIEGO, CA 92121-2133			CHOI, FRANK I	
			ART UNIT	PAPER NUMBER
			1616	

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/863,825

Applicant(s)

KRALL ET AL.

Examiner

Frank I Choi

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 4-53 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 4-53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicant is correct in indicating that Hoffman (US Pat. 4,359,454) was never substantively addressed as said reference was not intended to be part of the rejection and should not have been included in the statement of the rejection, as such, the finality of the prior Office Action is withdrawn and a modified version of the prior rejection pursuant to 35 USC 103(a) is set forth below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1,4-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berger et al. (US Pat. 5,998,472) in view of Hawkins et al. (US Pat. 3,591,676), Evans et al. (US Pat. 5,695,480), Tseng et al., Woodward, Clark et al. (US Pat. 5,981,621), Krall (US Pat. 4,713,235), Almen et al., EP 0 747 069, Leung et al. (US Pat. 5,328,687) and McIntire et al. (US Pat. 3,654,239) for the reasons of record set forth in the prior Office Actions and the further reasons below.

Berger et al. disclose a composition comprising the combination of C1 to C8 alkyl cyanoacrylate ester compositions which are polymerizable formulations comprising polymerizable cyanoacrylate ester monomers and/or oligomers and C10-C12 alkyl cyanoacrylate monomer or oligomer, plasticizer(s) and polymerization inhibitor(s), for example, acetic acid

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(Column 4, lines 50-68, Column 5, lines 1-45, Column 6, lines 26-65). Berger et al. disclose that the use of two different monomers provides enhanced flexibility of the polymer (column 7).

Hawkins et al. discloses the combination of methyl 2-cyanoacrylate with higher esters of 2-cyanoacrylic acid, including n-hexyl, which reduces the undesired tissue reactions of the methyl ester alone and the while providing better biodegradability than the higher esters alone (Column 2, lines 1-30).

Evans et al. teach a compositions and methods for embolizing blood vessels using microballoon catheters and treating arteriovenous malformations comprising a biocompatible prepolymer, such as a cyanoacrylate, which is preferably non-inflammatory, a contrast agent, such as gold, and optionally a biocompatible solvent (Column 1, lines 65-68, Column 2, lines 1-6, Column 3, lines 60-68, Column 4, lines 1-13, Column 5, lines 63-68, Column 6, lines 1-6, 26-36).

Tseng et al. teach that 2-cyanoacrylates are widely used in surgical fields as hemostatic agents and tissues adhesives, and have been used in the therapeutic embolization of arteriovenous malformation (pg. 65). It is taught that the physicochemical properties of 2-cyanoacrylates can be improved to obtain higher reliability by mixing with a contrast medium as they are not radiopaque, having appropriate viscosity and set time in blood, and low bonding strength so that the microcatheter is removed easily (Pgs. 65,66). It is taught that homologues of ethyl 2-cyanoacrylate and isobutyl 2-cyanoacrylate having a longer ester side group generate more flexible polymers than homologues with shorter ones (Pg. 66). Lipiodol ultra-fluide is taught as a suitable radiopaque material (Pg. 66).

Woodward teaches that hexyl 2-cyanoacrylate as compared to ethyl, butyl and octyl 2-cyanoacrylates stimulated only a transient inflammatory response (Abstract).

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Clark et al. teach that plasticizers, such as isopropyl myristate, impart flexibility to the polymerized cyanoacrylate monomer (Column 6, lines 21-30). It is taught that anionic stabilizing agents such as phosphoric acid, hydroquinone, and p-methoxyphenol, and mixtures thereof, inhibit polymerization (Column 6, lines 34-51, Column 18, Claim 17). It is taught that the stabilizing agent is present in the range of 20-200 ppm (Column 18, Claim 18).

Krall teaches method of sterilizing females using cyanoacrylates in the fallopian tubes (Column 5, lines 45-58).

Almen et al. teach that alkyl cyanoacrylates present a reasonable compromise between adhesive capabilities and toxicity and that the chemistry and use of the tissue adhesives have been extensively reviewed, including their use with magnetic powder to be guided and confined to the area of treatment (Pg. 348).

EP 0 747 069 teaches a medical device such as a stent or heart valve which is employed with polymer systems, such as cyanoacrylates (Column 3, lines 20-58, column 7, lines 56-58, column 8, lines 1-21, column 14, lines 19-39).

Leung et al. teach that alpha cyanacrylates are useful as tissue adhesives, sealants for preventing bleeding, covering wounds, delivery of therapeutic or other bioactive agents, apposing surgically incised or injured tissue and as implants (Column 3, lines 10-21, column 8, lines 21-68, column 9).

McIntire et al. teach that polymers of alkyl cyanoacrylates may be added to monomer alkyl cyanoacrylates to prevent undue escape of the adhesive from any given area and to allow sufficient time for the monomeric material to polymerize (column 1, lines 64-70, Column 2, lines 22-55).

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the use of mixtures of alkyl cyanoacrylates with a second component which includes an oligomer of alkyl cyanoacrylate, a plasticizer and opacificant agent. However, the same is amply suggested by the prior art as compositions and methods comprising alkyl

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cyanoacrylates, plasticizers and opacificant agents and methods for their use and the addition of polymers of alkyl cyanoacrylates as thickeners and mixtures of monomers of alkyl cyanoacrylates are disclosed in the art. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to use a two component composition of monomeric alkyl cyanocrylates and polymeric alkyl cyanocrylates with the expectation that the combination would prevent undue escape of the adhesive and allow sufficient time for the monomeric material to polymerize and that the use of two different monomers of alkyl cyanocrylates would result in a more flexible polymer having the desired properties of lower tissue reaction and higher biodegradability than single monomer compositions.

Examiner has duly considered Applicant's arguments but deems them unpersuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 231 USPQ 375 (Fed. Cir. 1986). Further, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 208 USPQ 871 (CCPA 1981).

Applicant makes argues that Evans does not teach or suggest all of the elements of the present invention. However, there is no requirement that each reference teach all the elements of the present invention so long as the combined teachings of all the references does teach or suggest all of the elements of the present invention. Evans is not being cited for the teaching of

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the combination cyanoacrylates and the other components but for the use of contrast agents, i.e. gold, in cyanoacrylate as well as various uses of cyanoacrylate compositions.

With respect to McIntire et al., Applicant again argues that said reference does not teach or suggests all of the elements of the present invention. However, as indicated above, there is not required. McIntire et al. is cited for the motivation to combine polymers of alkyl cyanoacrylates (which would include the oligomers of Berger et al.) to monomers of alkyl cyanoacrylates.

Contrary to Applicant's arguments, Berger et al. does suggest the combination of different C1-C8 monomers in addition to the combination with C10-C12 alkyl cyanocrylates (See Berger et al., Column 4, lines 63-68). In any case, the combination of monomers s expressly disclosed by Hawkins et al. Further, although Berger et al. does discloses preferred embodiments not having plasticizers, said references does disclose the use of plasticizers. Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994).

Applicant argues that Tseng and Woodward do not teach or suggest all of the elements of the present invention, however, as indicated above, teaching or suggesting all of the elements in a single reference is not required. Tseng and Woodward are cited for the reasons above.

Applicant argues that there is no motivation to combine the references, however, there is motivation as indicated above. There is no requirement that Clark itself provide the motivation to combine the use of plasticizers and stabilizing agent with cyanocrylate with a two component

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composition as set forth in the claims. In any case, the prior art does motivate the use of plasticizers and stabilizing agents in cyanoacrylate compositions of which the present invention is clearly a cyanoacrylate composition. To the extent Applicant is arguing that the prior art does not disclose a two component composition, the limitation “first component and a second component” does not patentably distinguish from the prior art. The end result is a composition, i.e. a mixture of the disclosed elements, which is suggested by the prior art. In re Gibson, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious).

Applicant’s argument as to Hoffman is moot as said reference is not part of the rejection herein.

Applicant’s arguments as to Almen, Leung and EP 0747069 again are arguments that said references do not teach or suggest all of the elements of the present invention. Again, the rejection is based on the combination of references and the fact that each of the references alone do not teach or suggest all of the elements of the present invention does not overcome the rejection herein. Almen, Leung and EP 0747069 are being cited for the reasons above.

Applicant argues that there is no reasonable expectation of success or suggestion to combine or modify the references. However, the prior art as indicated above disclose both the mixture of monomers to arrive at the desired reduction in toxicity and increase in biodegradability, the mixture of monomers with oligomers to arrive at the desired polymerization rate, the use of plasticizers to arrive at the desired flexibility and the use of opacifying agents to make the compositions radiopaque. As such, the each of the components of the present invention and the motivation to combine or modify the same are taught or suggested by the prior art. Thus, there is both reasonable expectation of success and motivation to arrive at the present invention.

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Applicant argues that none of the cited references anticipate the claimed invention. Anticipation implies a rejection under 35 USC 102. The present rejection is pursuant to 35 USC 103(a). The prior art as indicated above discloses or suggests the combination of all elements of the claimed invention, including the use of polymerization inhibitors. None of Applicant's claims require the use of 2-hexyl cyanoacrylate, including claim 5, which only lists said monomer as one of several cyanoacrylate monomers which are to be selected. Applicant's Specification defines "anionic environment" to include tissue or blood which the prior art compositions are designed to polymerize upon contact with the same to provide an occlusion and/or adhere tissues.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Conclusion


A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a flexible schedule. However, Examiner may generally be reached Monday-Friday, 8:00 am – 5:30 pm (EST), except the first Friday of the each biweek which is Examiner's normally scheduled day off.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Mr. Gary Kunz, can be reached at 571-272-0887. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

FIC

July 24, 2004



SABIHA QAZI, PH.D
PRIMARY EXAMINER